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Cardiac Metastasis from Medullary Thyroid Cancers with Long-Term Survival under Vandetanib

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Established Facts

- Cardiac metastases from thyroid cancers are uncommon with a poor prognosis.

Novel Insights

- Our work highlights 2 major points:
- The diagnostic challenge represented by cardiac metastases: in both cases, the diagnosis was based on conventional imaging and originally confirmed by functional imaging with an immuno-PET scan using anti-CEA bispecific antibody and ⁶⁸Ga-labeled peptide which is the ultimate evidence of the medullary thyroid origin.
- The long-term survival of 2 patients who have developed cardiac metastases from MTC, in the current era of personalized medicine with targeted therapy, has never been described in the previous literature.

Keywords

Medullary thyroid cancers · Cardiac metastasis · Rearranged during transfection inhibitors · Vandetanib · Rearranged during transfection mutation

Abstract

Background: Cardiac metastases from thyroid cancers are uncommon with a poor prognosis. There is a lack of long-term follow-up studies. **Cases:** We report 2 cases of cardiac

metastasis from medullary thyroid cancer (MTC). Both patients presented limited metastatic disease apart from a cardiac metastasis. The initial diagnosis was challenging and was facilitated by functional imaging with an immuno-PET-CT using an anti-CEA bispecific antibody and a ^{68}Ga -labeled peptide. Both patients were treated with the multitarget kinase inhibitor vandetanib with prolonged stability. The first patient was alive at the last follow-up, 14 years after the diagnosis of cardiac metastasis. The second patient required surgical excision of the cardiac mass because of disease progression under vandetanib. **Conclusion:** These cases illustrate long-term survival and effectiveness of clinical management of 2 patients who developed cardiac metastases from MTC, in the current era of personalized medicine with targeted therapy.

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Introduction

Cardiac metastases from medullary thyroid cancers (MTC) are uncommon. Their frequency in large autopsy series in patients with thyroid cancers is low, between 0 and 5% [1–5]. Given the rarity of this metastatic location, the outcome remains unclear. The average length of survival is short, especially in patients with symptomatic and unresectable cardiac metastases [6]. This poor prognosis paradigm may be reconsidered in the light of current available therapies. We report here 2 cases of MTC cardiac metastasis with long-term outcome under the tyrosine kinase inhibitor vandetanib.

Patient 1

A 45-year-old woman was diagnosed with MTC after total thyroidectomy and neck dissection (Fig. 1a). Histology revealed an 11-mm thyroid tumor with minimal extra-thyroidal extension and massive lymph node metastases pT1b(s)N1b (AJCC/TNM cancer staging system 8th edition) [7]. Germline REarranged during Transfection (*RET*) gene analysis was negative. After a 3-year period of complete remission (calcitonin: 1 pg/mL), a progressive rise in calcitonin (up to 945 pg/mL, normal value <10 pg/mL) and carcino-embryonic antigen (CEA) (up to 8.5 ng/mL, normal value <5 ng/mL) levels led to the diagnosis of costal metastases treated with external beam radiation and surgery, 8 years after initial diagnosis. Two years later, a rise in calcitonin and CEA levels (1,390 pg/mL and 25 ng/mL, respectively) led to the diagnosis of a 21-mm

liver metastasis and a 30-mm cardiac mass in the right ventricular apex. A DOPA (6-[^{18}F]-L-fluoro-L-3, 4-dihydroxyphenylalanine) PET-CT and an immuno-PET-CT using an anti-CEA bispecific antibody and a ^{68}Ga -labeled peptide revealed cardiac uptake, leading to the diagnosis of MTC metastasis. Because of this threatening cardiac location and as an alternative to high-risk surgical treatment, radioimmunotherapy with iodine-131-labeled anti-CEA antibodies was performed. Two years after the cardiac metastasis diagnosis, the liver metastasis increased in size significantly and reached 26 mm with an increase in calcitonin and CEA levels (19,662 pg/mL and 46 ng/mL, respectively), and the patient was treated with vandetanib (300 mg/day), initially in a research protocol [8]. Notwithstanding the comparability between the different images performed, the cardiac metastasis remains globally stable after radioimmunotherapy. The liver metastasis, taken as a target lesion, decreased in size until complete response according to RECIST1.1 assessments, 7 years after the initiation of vandetanib. The cardiac metastasis decreased slightly on CT (–4 mm). No cardiologic metastatic-related symptom was reported from the diagnosis. Vandetanib was responsible for moderate toxicity: asthenia, increase in the QTc interval (460–511 ms), and photosensitization with the need for transitory withdrawal and/or reduced dosage. Finally, 10 years after its initiation, vandetanib was stopped because of severe functional renal failure. The evaluation at 2.5 years after vandetanib withdrawal showed a stable disease on imaging with stable tumoral marker levels (calcitonin at 272 pg/mL and CEA at 31 ng/mL), and the patient was still free of cardiologic symptoms.

Patient 2

A 63-year-old woman was treated for a sporadic MTC with total thyroidectomy and neck dissection (Fig. 1b). Histology revealed a multifocal tumor with a foci of 20 mm in maximum diameter invading almost the entire lobe with minimal extra-thyroidal extension and massive lymph node metastases pT2(m)N1b [7]. After the initial surgery, serum calcitonin level dropped from 336 to 17 pg/mL. Three years later, calcitonin levels rose to up to 164 pg/mL, leading to the diagnosis of lymph node metastases treated by 2 additional neck surgeries. Two years later, calcitonin and CEA levels increased (751 pg/mL and 14.5 ng/mL, respectively). A chest CT showed micronodular lung and liver metastases and a suspicious 65-mm myocardial mass in the right atrioventricular groove in-

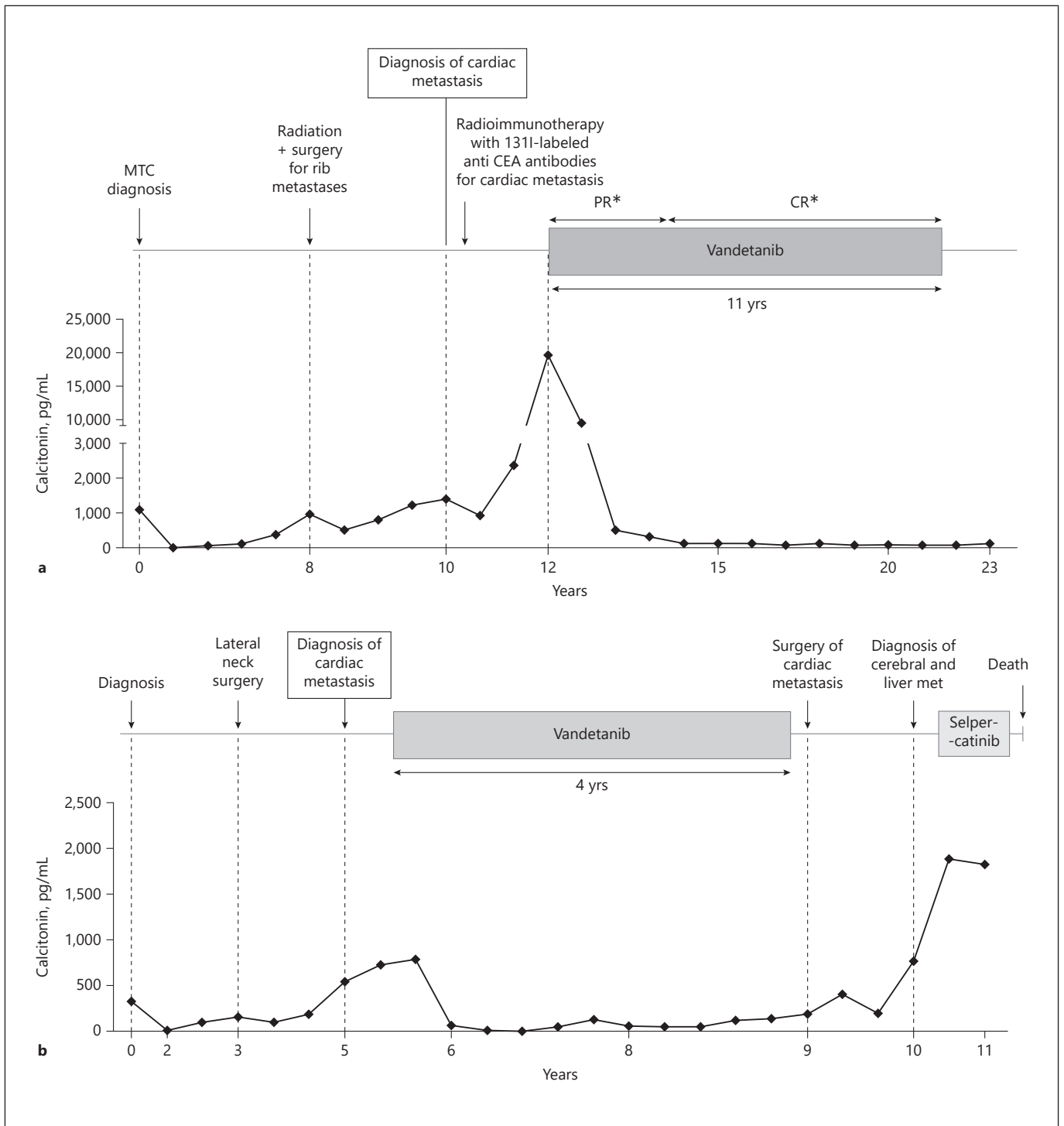
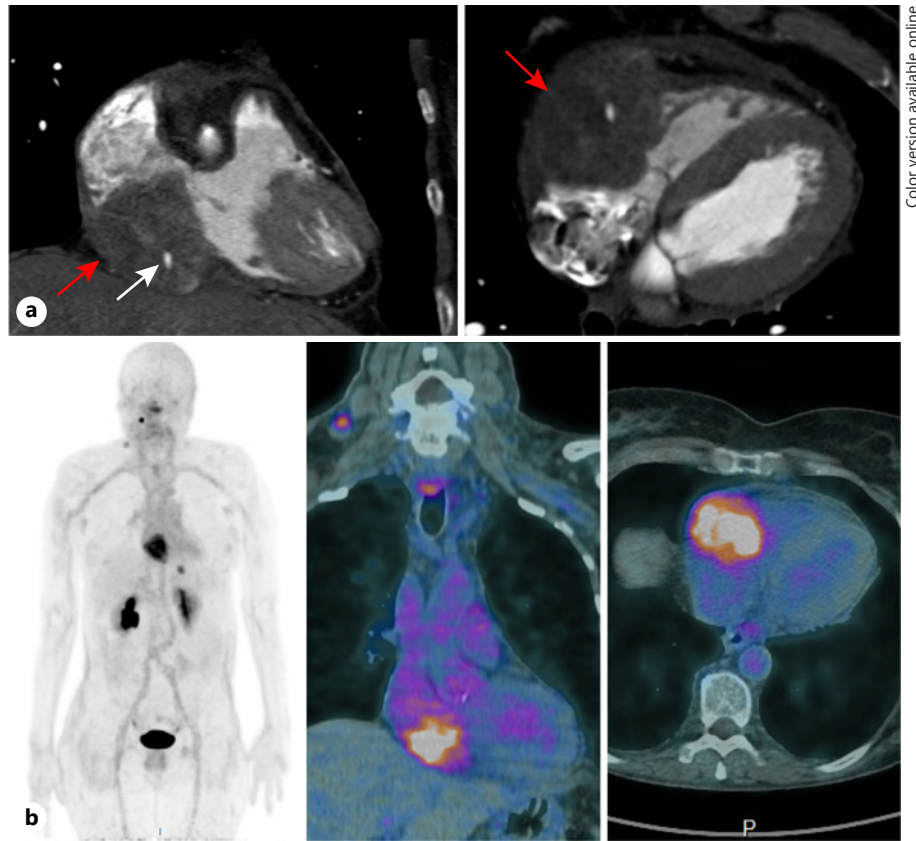


Fig. 1. Clinical and biochemical evolution of patient 1 (a). Clinical and biochemical evolution of patient 2 (b). MTC, medullary thyroid cancer; PR, partial response; CR, complete response. *The target lesion was a liver metastasis.



Color version available online

Fig. 2. **a** Cardiac CT in the coronal plane (left panel) and in the sagittal plane (right panel) showing the thyroid metastasis (red arrow) encasing the right ventricle and the right atrium with the right coronary artery (white arrow) encompassed by the tumor. **b** Planar image (left panel) and fused images (right panel) of an immuno-PET scan using an anti-CEA bispecific antibody and a ^{68}Ga -labeled peptide revealing cardiac uptake of the metastatic lesion with a right lateral neck and mediastinal lymphadenopathies and a liver metastasis.

vading the pericardium, the ipsilateral atrial and ventricular cavities, and the tricuspid valve confirmed by a dedicated MRI (Fig. 2a). An F-DOPA PET-CT and ^{111}In -octreoscan revealed a weak uptake of the cardiac mass. An immuno-PET-CT using an anti-CEA bispecific antibody and a ^{68}Ga -labeled peptide (IMP288), performed within a clinical trial (NCT01730638), also revealed a cardiac uptake confirming the metastatic nature of the mass (Fig. 2b). At that time, there was no cardiac metastasis-related consequence. The decision to perform a surgical resection was rejected given the unfavorable benefit-risk balance. Vandetanib (300 mg/day) was initiated, and a partial regression of the cardiac metastasis was observed ($\sim 30\%$ in 8 months) and a decrease in cervical lymph node and lung metastases. Vandetanib dosage reduction was necessary because of a prolonged QTc interval 9 months after its introduction. Progressively, calcitonin and CEA levels rose again (422 ng/mL and 13.9 pg/mL, respectively) in parallel with significant progression of the cardiac mass responsible for an atrioventricular obstacle and a low flow. Vandetanib was discontinued 3.5 years after its initiation, and wide surgical resection of the cardiac metastasis was performed with tricuspid biopro-

thetic valve replacement. Histological analysis confirmed MTC metastasis with the proliferation marker Ki67 between 5 and 10%. Given the partial metastasis resection, the progression of calcitonin to up to 199 pg/mL, 5 months after the cardiac surgery, and the presence of a *RET* M918T somatic mutation, a treatment with cabozantinib was initiated (60 mg/day). However, due to a decrease in left ventricular function, cabozantinib was stopped 3 weeks later. As calcitonin and CEA levels decreased after these few weeks of treatment and because of the patient wish, the option of active surveillance was chosen. Unfortunately, 1 year later, new hepatic and brain metastases (right 25-mm frontal-parietal and left occipital lesions of few millimeters) were diagnosed in the workup of myoclonic seizures of the left hand. This diagnosis was accompanied by general progression of the metastatic disease (cardiac, pulmonary, and cervical lymph node metastases) along with calcitonin and CEA levels (respectively, 1,892 ng/mL and 146 pg/mL). Stereotaxic radiation therapy by CyberKnife[®] was performed on brain metastases. The patient was included in a phase 1–2 trial evaluating the highly specific RET inhibitor selpercatinib [9]. Five weeks after selpercatinib initiation, the patient developed

a confusional state. The MRI performed 8 days later revealed a worsening of a perilesional cerebral edema. The patient died 2 weeks later from brain herniation related to an increased vasogenic fronto-parietal edema with a mass effect on the right lateral ventricle.

Discussion

We report here 2 cases of unusual metastatic location of MTC. Giuffrida and Gharib [10] and Catford et al. [6] reviewed the literature of thyroid cancer cardiac metastasis. In the latest review, 59 cases were identified over a 130-year period. The most common histological type is anaplastic thyroid cancer, closely followed by follicular thyroid cancer. Overall, the prognosis would appear poor [6]. Ten other cases of cardiac metastases have been reported since the last review [11–20], mostly from poorly differentiated or papillary carcinoma with aggressive features.

Only 3 cases of MTC cardiac metastasis have been reported [20–22]. One of them was our first patient reported in 2010 but without any outcome data [22]. The diagnosis of cardiac metastasis remains challenging. Ultrasonography, CT, or MRI is recommended in the first line [6]. MRI appears to be superior to ultrasound in the detection of cardiac metastases [23, 24]. Some have suggested that echocardiography perfusion imaging could be used to provide information on the vascularization of the mass, helping to differentiate malignant from benign lesions [25]. Others have suggested that ^{18}F -FDG uptake on a PET-CT could be valuable to differentiate between benign, primary malignant, and metastatic cardiac tumors [26, 27]. In the cases reported here, the endocrine nature of the cardiac mass was suggested by abnormal uptake on the F-DOPA PET scan and ^{111}In -octreoscan. In both cases, iodine-131-labeled anti-CEA antibody uptake in the cardiac mass on an immuno-PET scan was the ultimate evidence of the medullary thyroid origin.

Patient-reported outcome in the literature is available for 1 MTC cardiac metastasis, with death 1 year after the diagnosis of the cardiac lesion [21]. The threatening metastatic location of our 2 patients motivated the introduction of a targeted therapy. The prolonged survival under vandetanib is a notable feature which has never been reported in MTC. Surgery initially recused in our second patient became finally mandatory despite the complexity of the procedure, as threatening cardiac-related symptoms occurred. The highly potent and selective RET inhibitors such as pralsetinib [9, 28] and selpercatinib [29]

represent promising treatments in patients with driven RET-altered tumors and are currently tested, as first-line therapy, in worldwide phase 3 trials. The risk of cardiac rupture in case of rapid and important tumor regression remains an open question.

The conventional paradigm of short-term prognosis for patients who develop MTC cardiac metastases should be revised in the light of these new targeted therapies. Positive diagnosis remains challenging, but new functional imaging should allow recognizing the metastatic nature of a cardiac mass. In terms of clinical management, based on our experience, cardiac surgery is still indicated whenever technically feasible in case of cardiovascular impairment. However, when necessary, specific RET inhibitors should be considered based on their high efficacy and the lack of cardiovascular toxicity [9].

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Statement of Ethics

Informed consent has been obtained from both patients for publication of the case report and accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Contribution to the conception of the work: C.B., L.G., S.L., and M.S. Analysis or interpretation of data for the work: L.C., F.K.B., C.B.M., A.D., P.L., and O.H. Drafting the work: C.B., L.G., S.L., and M.S. Revising the work for important intellectual content: C.B., L.G., S.L., M.S., L.C., F.K.B., C.B.M., A.D., P.L., and O.H. Final approval of the version to be published: C.B., L.G., S.L., M.S., L.C., F.K.B., C.B.M., A.D., P.L., and O.H. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: C.B., L.G., S.L., M.S., L.C., F.K.B., C.B.M., A.D., P.L., and O.H.

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